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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/697,716	10/31/2003	H. William Bosch	029318-0977	8372

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EXAMINER	
JEAN-LOUIS, SAMIRA JM	

ART UNIT	PAPER NUMBER
1617	

MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/697,716	BOSCH ET AL.	
	Examiner	Art Unit	
	SAMIRA JEAN-LOUIS	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 November 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-41 and 43-108* is/are pending in the application.

4a) Of the above claim(s) *8,15,16,23-27 and 48-108* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7,9-14,17-22 and 28-47* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *Sheets (2)*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendment

This Office Action is in response to the amendment submitted on 11/26/2007. Claims 1-41 and 43-108 are pending in the applications, with claims 8, 15-16, 23-27, 48-108 having being withdrawn. Accordingly, claims 1-7, 9-14, 17-22, and 28-47 are being examined on the merits herein.

Receipt of the aforementioned amended claims is acknowledged and has been entered.

Examiner further acknowledges amendment of claims 14, 39-40 and cancellation of claim 42 and consequently the rejection under 35 U.S. C. 112, second paragraph has been withdrawn. However, due to the presence of the undefined word "bioequivalency" in quotation marks in claim 43, the rejection of claim 43 under 35 U.S.C. 112, 2nd paragraph is still maintained.

Applicants traversal of the provisional ODP rejection of claims 1, 4-7, 9-12, 14, 18-21, and 28-47 over claims 1-15, 17-20, and 22-41 of copending application 10/683154 is acknowledged, but since applicant did not put forth any arguments against this rejection, the ODP is maintained for reasons of record as stated in the previous office action and restated below for applicant's convenience.

Applicant's arguments against the 35 USC 102(b) rejection of claims 1-5, 7, and 9-13 over Krause et al. is not persuasive. Applicant argues that Krause does not teach triamcinolone particles of less than 2000 nm and that the particles are not in crystalline form. Specifically, Krause teaches nanoparticles of

polylactic acid (PLA) particles loaded with triamcinolone acetonide where the loaded particles possess a mean diameter below 1 micron. While Krause does not explicitly states the size of the triamcinolone particles, it is inherently interpreted that given the triamcinolone drug are encapsulated inside the PLA, thus the particle size of the drug is necessarily below 1 micron (see abstract, line 6) and this meets the limitation of claim 1 as previously presented. Moreover, it is noted that In re Best,195 USPQ 430, and In re Fitzgerald, 205 USPQ 594, discuss the support of rejections wherein the prior art discloses subject matter which there is reason to believe inherently includes functions that are newly cited or is identical to a product instantly claimed. In such a situation the burden is shifted to the applicants to "prove that subject matter shown to be in the prior art does not possess characteristic relied on" (205 USPQ 594, second column, first full paragraph).

Applicant's contention that the triamcinolone acetonide of Krause is not in crystalline form is not found persuasive because Krause clearly points out that the PLA encapsulated triamcinolone acetonide retarded drug release in comparison to microcrystalline triamcinolone acetonide in all cases (i.e. both encapsulated and non-encapsulated triamcinolone acetonide; see abstract, lines 8-10). Moreover, Krause further teaches that during the first hour after injection of the PLA particles, a burst effect occurred possibly as a result of drug lying beneath the surface of the nanoparticles which may be dissolving faster than drug crystals that are embedded in the center of the sphere (see pg. 152, lines

15-17). As a result, crystal drug form necessarily meets the limitation of claim 4 as previously presented.

Applicant's argument that the German Patent Beck teaches polylactic acid particles of micron-sized particles and not particle size particles is moot given that Beck suggests the use of small PLA particles for increased drug distribution and Krause specifically teaches the use of small nanoparticles for increased efficiency of drug distribution based on a modified procedure of Beck (see pg. 146, lines 15-24). In view of applicant's amendment to the claims the 35 USC 102(b) rejection is withdrawn and a 103(a) rejection of these amended claims is now made.

Applicant's argument to claims 6, 14, 17-22, and 28-47 rejected under 35 U.S.C. 103 (a) for obviousness over US. Patents, 5,049,389, 5,043,165, and 5,744,155 for not including any independent claim in the obviousness rejection set forth is acknowledged and is found persuasive. Consequently, the 103 (a) rejection is withdrawn.

In view of applicant's amendment, the following modified 103 (a) Non-Final rejections are being made.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to

be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-5, 7 and 9-14 and 18-21 and 28-41, and 43-47 are rejected under 35 U.S.C. 103 (a) as being unpatentable over Krause et al. (Int. Journal of Pharmaceutics, 1985, Vol. 27, pg. 145-155, already cited by applicant on an IDS 1449 form) in view of Radhakrishnan (U.S. 5,049,389, previously presented).

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Krause et al. teaches a composition of polylactic acid (PLA) (i.e. interpreted as a stabilizer given that applicant did not explicitly define a stabilizer as solely a surfactant) loaded with microcrystalline salts of triamcinalone acetonide (instant claims 1 -3; see abstract). It is also interpreted that loading of

triamcinalone acetonide entails both encapsulation and adsorption of PLA unto triamcinolone acetonide given that fig. 2 denotes a transectional view of PLA nanoparticle with the triamcinolone crystals embedded in the center of the sphere and given that Krause suggests drug lying beneath the surface of the nanoparticles dissolve faster than drug crystals (i.e. crystalline form; instant claims 1 and 4) embedded in the center of the spheres (see pg. 145, microcrystalline form, abstract lines 8-10; see pg. 150, fig. 2 and pg. 152, lines 15-17). Krause et al. further teaches that the PLA nanoparticles have a mean diameter below 1 micron suggesting that the nanoparticle size of the triamcinolone acetonide necessarily are below 1 micron as well and this meets the limitation of claims 1 and 5 (see abstract). Krause et al. also teaches a drug content from 2.9% to 8.8% w/w (instant claim 10) and the inclusion of gelatin solution (i.e. additional stabilizer, instant claims 11-14) at 0.5% w/w and water as a suspension carrier (instant claim 9; see abstract and preparation of PLA nanoparticles-pg 147). Additionally, the composition of Krause et al. can include excipients (i.e. buffers; instant claim 9) and can be formulated for intravenous injection (i.e. liquid suspension; instant claim 7; instant claim 6 for parenteral species; see abstract and pg. 147, drug release section, lines 3 and 11 and size distribution section, line 1). Krause et al. also teaches a suspension of various sized nanoparticles (i.e. triamcinalone of different sizes as well) in a solution (see size distribution, pg. 147 and table 1) that was injected into rats and subsequently dispersed to the liver and lung where high levels were still detected after 2 hours; this suggests that the ability of the nanoparticles to adhere to the

surface of the liver and the lung is well enhanced (i.e. bioadhesive, instant claims 18-19; see pg. 153, table 2). Finally, Krause et al. discusses the fact that increasing PLA concentrations can result in an increase in viscosity (instant claim 44; see pg. 149, lines 16-17).

Krause et al. does not specifically teach a composition comprising triamcinolone acetonide in combination with other anti-inflammatory drugs or a composition that redisperses upon administration to a size less than 2000 nm. Moreover, Krause et al. does not specifically teach particles of triamcinolone acetonide with a particular percentage of Tmax, Cmax, AUC, viscosity or bioequivalency.

Radhakrishnan, however, teaches encapsulated steroidal compositions such as triamcinolone and its salts or esters in combination with non-steroidal drugs such as anti-inflammatory agents or antiviral drugs (i.e. acyclovir, non-elected species in claim 21, col. 20, line 43) or anti-hypertensive drugs (i.e. enalapril, verapamil, non elected species in claim 21, col. 20, lines 50-51; instant claims 20-21 col. 20, lines 14-15 and lines 31-32). Radhakrishnan further teaches the steroidal composition in deionized water (i.e. biorelevant media; instant claims 30-31; see col. 28, line 17). Radhakrishan also teaches encapsulated steroids of nanoparticle size where the mixture is filtered over a filter with pore size smaller than steroid crystals (i.e. non-encapsulated steroid crystals) usually of 0.1-1 micron filter. Subsequently, the filter is discarded

leaving the micelle filtrate (i.e. encapsulated steroidal drug of 1 micron or less; see col. 14, lines 64-68).

Regarding the redispersibility of the triamcinolone particles, Krause et al. did teach that the particles do possess minute diameters. Consequently, it is well within the purview of one of ordinary skill in the art to conclude that given that that these drugs are small and are able to redistribute to the lung and liver as disclosed by Krause et al., it would have been obvious to one or ordinary skill in the art at the time of the invention that the triamcinolone particles would also redisperse at the same small size of less than 1 micron and this meets the limitation of claims 28-32.

Thus, to one of ordinary skill in the art at the time of the invention would have found it obvious to combine the anti-inflammatory agents of Radhakrishnan into the composition of Krause et al. since encapsulation of the drugs would lead to an improved delivery of the non-steroidal drug. Given that Krause et al. teaches a composition of polylactic acid (PLA) loaded with microcrystalline salts of triamcinalone acetonide, and Radhakrishan et al. teaches that inflammatory drugs can be combined with encapsulated triamcinolone compositions for efficient drug target delivery, one of ordinary skill would have been motivated to combine an anti-inflammatory drug of Radhakrishan with the composition of Krause et al. with the expectation of providing a composition that is efficient in delivering drugs to targeted tissues.

Regarding the Tmax , Cmax, viscosity, bioequivalency and AUC of the triamcinalone particles as recited in claims 33-41 and 43-47, it is considered that one of ordinary skill in the art at the time of the invention was made would have found it obvious to conclude that the composition of Krause et al. combined with the anti-inflammatory agents of Radhakrishan et al. would possess the same pharmacokinetic profiles as that disclosed by the applicant given that these characteristics are physical properties of the compound (i.e. nanoparticles of triamcinalone acetonide disclosed by Krause et al.) and such property is inseparable from the parent compound.

It is further noted that In re Best,195 USPQ 430, and In re Fitzgerald, 205 USPQ 594, discuss the support of rejections wherein the prior art discloses subject matter which there is reason to believe inherently includes functions that are newly cited or is identical to a product instantly claimed. In such a situation the burden is shifted to the applicants to "prove that subject matter shown to be in the prior art does not possess characteristic relied on" (205 USPQ 594, second column, first full paragraph).

Claims 6, 17, and 22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Krause et al. (Int. Journal of Pharmaceutics, 1985, Vol. 27, pg. 145-155, already cited by applicant and provided on an IDS 1449 form) in view of Radhakrishnan (U.S. 5,049,389, previously presented) as

applied to claims 1-5, 7 and 9-14 and 18-21 and 28-41, and 43-47 above and in further view Unger et al. (U.S. 5,542,935).

The Krause and Radhakrishnan references are as discussed above and incorporated by reference herein. However, Krause and Radhakrishnan do not address the aforementioned composition for topical administration. Similarly, Krause and Radhakrishan did not specifically disclose specific anti-inflammatory agents such acetylsalicylate elected by applicant or the preferred stabilizers of applicant.

Unger et al., however, teaches encapsulation of therapeutic drugs (see abstract). Suitable therapeutic agents include steroidal drugs such as triamcinalone or triamcinalone acetonide in microspheres or liposomes (see col. 24, line 16 and col. 25, lines 9-11) and non-steroidal drugs such as aspirin and salicylates (i.e. acetylsalicylate, instant claim 22; see col. 25, lines 37-38). Unger et al. also teaches that if desired more than one therapeutic agent may be encapsulated for co-administration (see col. 23, lines 55-56 and col. 26, lines 34-37). Additionally, emulsifying agents and/or solubilizing agents may be used in conjunction with the liposome (i.e. capsule) including sodium lauryl sulfate (instant claim 17; see col. 23, lines 30-32 and line 40). Moreover, Unger et al. teaches that the encapsulated therapeutic drugs may be administered topically (instant claim 6; see col. 31, lines 15-17).

Thus, to one of ordinary skill in the art at the time of the invention would have found it obvious to utilize acetylsalicylate into the composition of Krause et al. and applied it topically given that Unger et al. teaches co-administration of salicylate with triamcinolone acetonide in encapsulated compositions. Likewise, it would have been obvious to utilize the emulsifying agent, sodium lauryl sulfate, since Unger et al. teaches its use in encapsulated compositions employing the steroid triamcinolone acetonide. Given that Krause et al. teaches a composition of polylactic acid (PLA) loaded with microcrystalline salts of triamcinalone acetonide, and Radhakrishan et al. teaches that inflammatory drugs can be combined with encapsulated triamcinolone compositions for efficient drug target delivery, and Unger et al. teaches the use of the emulisifyer, sodium lauryl sulfate and salicylate in conjunction with triamcinalone acetonide, one of ordinary skill would have been motivated to add the salicylate and emulsifier sodium lauryl sulfate of Unger et al. into the composition of Krause and Radhakrishan with the expectation of providing a topical composition of Krause et al. that is stable and efficient in delivering drugs to targeted tissues.

Provisional Non-Statutory Double Patenting

Claims 1, 4-7, 9-12, 14, 18-21, and 28-47 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-15, 17-20, and 22-41 of copending Application No. 10683154 (hereinafter Liversidge US Patent Application No. '154). Although the conflicting claims are not identical, they are not patentably distinct from each other because

both applications are directed to a composition comprising effective nanoparticle size of a drug characterized by desirable pharmacokinetic profiles: effective particle size after redispersibility (see claims 28-32 of instant application vs. claims 22-26 of Liversidge '154), T_{max} (see claims 33-34 of instant application vs. claims 27-28 of Liversidge '154), C_{max} (see claims 35-36 of instant application vs. claims 29-30 of Liversidge '154), higher AUC rate (see claims 37-40 of instant application vs. claims 31-34 of Liversidge '154), bioequivalent (see claims 41-43 vs. claims 35-37 of Liversidge '154) as well as viscosity (see claims 44-47 of instant application vs. claims 38-41 of Liversidge '154), all of which are due to the size of the drug.

More specifically, claims 1, 4-7, 9-12, 14, 18-21, and 28-47 of the instant application are directed to a composition comprising: sterol (triamcinalone acetonide being the elected species) with particle size less than 2000nm and a surface stabilizer.

Claims 1-15, 17-20, and 22-41 of the conflicting Liversidge '154 application are directed to a composition comprising an anti-fungal drug with particle size less than 2000nm and a surface stabilizer (other than non-ionic).

As a result, although claims 1, 4-7, 9-12, 14, 18-21, and 28-47 of the instant application are not identical to claims 1-15, 17-20, and 22-41 of the conflicting Liversidge '154 application, the aforementioned claims are not patentably distinct from each other because said claims comprise nanoparticle drugs of a size less than 2000nm characterized by increased bioavailability and redispersibility, which results in better efficacy of both drugs. Thus, one of

ordinary skill would have the motivation to use "any" nanoparticulate of a drug with a stabilizer and would have a reasonable expectation that such a substitution would yield predictable results, including an enhanced pharmacokinetic profile. Thus, the aforementioned claims of the instant application are substantially overlapping in scope as discussed hereinabove and are prima facie obvious over the cited claims of corresponding application No. 10, 683, 154.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Samira Jean-Louis whose telephone number is 571-270-3503. The examiner can normally be reached on 7:30-6 PM EST M-Th.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on 571-272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/S. J. L. /

Examiner, Art Unit 1617

03/04/2008

/SREENI PADMANABHAN/

Supervisory Patent Examiner, Art Unit 1617